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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,499	12/17/2001	Stephen B. Liggett	MWH-0031US	4401

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GENAISSANCE PHARMACEUTICALS
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,499	LIGGETT, STEPHEN B.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *6-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5* is/are rejected.

7)☒ Claim(s) *2-4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1201* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *1449: 3/03* .

DETAILED ACTION

1. This action is in response to the papers filed April 25, 2002. Currently, claims 1-14 are pending. Claims 6-14 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election with traverse of Group I (Claims 1-5) in the paper filed April 25, 2003 is acknowledged.

The response traverses the restriction requirement because there is a technical relationship among the inventions of Groups I, II and III which link the inventions.

According to PCT Rule 13.2, unity of invention exists only when there is a shared same or corresponding special technical feature is a contribution over the prior art. The inventions listed in Group I do not relate to a single general inventive concept because the lack of the same or corresponding special technical feature. The technical feature of Group I is the association of a T at position 491 of the B2AR cDNA as indicative of poor bronchodialating response to an agonist which is shown by Green et al. (J. of Biol. Chem. Vol. 268, No. 31, pages 23116-23121, 1993) to lack novelty or inventive step and does not make it a contribution over the prior art.

While the response argues there is the same or corresponding special technical feature, this feature is not a contribution over the prior art. Moreover, the response restates the claims and states there is a link in general inventive concept. The presence of a polymorphism at position 491 is not a contribution over the art, as exemplified by Green et al and others. Moreover, Green specifically studies the

activation of B2AR by agonists. Therefore, there is no shared special technical feature among the groups and the lack of unity requirement is appropriate.

Claims 6-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

This application contains claims 6-14 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application is a 371 application of PCT/US00/06502, filed March 10, 2000 and claims priority to provisional application 60/124,060, filed March 1999.

The first line of the specification contains a reference to the provisional application, however the reference indicates that the provisional was filed in 2000. The oath indicates that the provisional application was filed in 1999. Appropriate correction is required.

Drawings

4. The drawings are acceptable.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other

information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The list of references may be found on pages 17-18 of the specification. While many of the references are listed on an IDS form, not all of the references are found on the IDS. For example, reference number 12 is not located on an IDS form.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 5 is indefinite over the recitation "the patient's genotype" because Claim 1 does not refer to a patient. Claim 1 is directed to an individual. Thus, "the patient's genotype" lacks proper antecedent basis. This rejection may be easily overcome by amending Claim 5 to recite the "individuals" genotype. Moreover, the claim recites "at a position corresponding to the +491PS in the two copies." It is unclear whether the claim is intended to require determining the nucleotides present at position 491 of the B2AR gene or whether the claim is directed to detecting another nucleotide which "corresponds" to 491. The specification does not teach what is meant by

"corresponds." Therefore, it is unclear what is mean by corresponding. Thus, as written, the metes and bounds of the claimed invention are unclear. The rejection may be easily overcome by amending the claim to delete "corresponding to" such that is it clear that the identity of position 491 is detected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (J. Biol. Chem. Vol. 268, No. 31, pages 23116-23121, 1993) as evidenced by Lobb et al (US Pat. 5,871,734, Feb. 1999) and in view of Tan et al. (Lancet, Vol. 350, page 995-999, October 1997) or Drazen et al (US Pat. 6,156,503, December 2000).

Green et al. (herein referred to as Green) teaches a polymorphisms within the fourth transmembrane domain which alter ligand binding and functional properties of the human B2Adrenergic Receptor. Green discusses the consequences of a single polymorphism at nucleic acid 491 where a thymidine was found to be substituted for a cystidine, resulting in the substitution of Ile for Thr at amino acid residue 164 (page 23117, col. 1). The mutation at Thr164Ile was analyzed and decreased affinity was found with the catecholamines isoproterenol and norephinephrine. Agonist-dependent

parameters were examined including activation of adenylyl cyclase and receptor sequestration (page 23118, col. 1). The results are shown in Figure 2 which illustrates an approximately 3-fold rightward shift in the epinephrine dose-response curve and a decrease in maximal stimulation of adenylyl cyclase for Ile164 versus WT B2AR (page 23118, col. 1). The depressed agonist-stimulated adenylyl cyclase activity of Il164 was demonstrated for epinephrine (a bronchodialator). Green analyzes the mechanisms of receptor sequestration of Ile164 in response to saturating concentrations of epinephrine. The exposure of Ile164 to epinephrine resulted in about 65% less maximal sequestration as compared to the wild-type (page 23119, col. 1).

Lobb et al (US Pat. 5,871,734, Feb. 1999) teaches "early treatments for asthma focused on bronchoconstriction and led to the development of many effective bronchodilator drugs. The most commonly prescribed were beta2-adrenoceptor agonist (epinephrine, isopoternol, albuterol, salmeterol, etc)" (col. 1-2, lines 65-5).

Neither Green nor Lobb specifically teach using the genotype at position 491 to predict an individual's bronchodilating response to an agonist of B2AR.

However, Tan et al. (herein referred to as Tan) teaches an association between B2adrenoceptor polymorphism and susceptibility to bronchodilator desentisation in asthmatics. While Tan analyzes polymorphisms at codons 16 and 27, Tan specifically illustrates that individuals with various polymorphisms can be characterized based upon the allele present.

Moreover, Drazen claims a method of method of identifying individuals susceptible to adverse responses to regular beta-agonist administration, the method

comprising steps of: i) providing a genomic nucleic acid sample from an individual; ii) identifying in said sample a first and second allele of the individuals beta2 -adrenergic receptor gene; and iii) classifying the individual as susceptible to adverse responses to regular .beta.-agonist administration if the first and second alleles of the beta2 -adrenergic receptor gene both encode Arg at residue 16 of the beta2 -adrenergic receptor protein.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have used the experimental information of Green which demonstrates a poor bronchodilating response to epinephrine to predict an individuals response to an agonist based upon the allele present as taught by Tan or Drazen. While Green specifically demonstrates an association of Ile164 with poor bronchodilating response to epinephrine, Green does not specifically teach using the information do characterize individuals for the response. Tan, however, analyzes asthmatic patients for their genotype and response to a randomized double-blind, placebo-controlled, cross-over study to conclude that B2AR polymorphisms were associated with bronchodilation response. Once an association between a genotype and a trait is provided, using the information to predict an individual's predisposition to the condition would be obvious in light of the teachings that people use genotypes to assess patients. Thus, given the strong experimental data of Green, the ordinary artisan would have been motivated to have used the information of Green to analyze individuals for bronchodialting response to epinephrine, as taught by Tan or Drazen.

With respect to Claim 5, Tan specifically teaches determining whether the individual is homozygous or heterozygous for a specific allele. Moreover, since Green specifically teaches that the presence of a T is indicative of poor bronchodilating response, the ordinary artisan would have been motivated to have determined whether either of an individual's alleles was a T. Without determining both copies of an individuals alleles would possibly lead invalid results, as the first copy of the gene typed may be a C, however, the second copy may be a T. Thus, the presence of a T would be indicative of a poor bronchodilating response. Therefore, detecting a T at position 491 of B2AR would have indicated to the ordinary artisan that an individual was likely to exhibit a poor bronchodilating response to the agonist.

Allowable Subject Matter

8. Claims 2 and 3 are drawn to specific agonists of B2AR. These agonists, while known in the art as agonists of B2AR, the art does not teach nor suggest the correlation between a T at position 491 of B2AR and a poor bronchodilating response to the agonist. The instant specification specifically teaches and illustrates in Figure 6, the differences in Thr164 and Ile164 bronchodilating response to an agonist. Each of salmeterol, albuterol, metaproterenol, terbutaline and formoterol were analyzed and showed a decrease in response to the agonist. Thus, the art, neither teaches nor suggests the presence of a T at position 491 of B2AR and a poor bronchodilating response to the specified agonist. Moreover, Claim 4 depends from Claim 3.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
September 5, 2003